Complementary Therapies in Clinical Practice 23 (2016) 130–135

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp

The effect of Hop (*Humulus lupulus L.*) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial

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ARTICLE INFO

Article history:
Received 16 January 2015
Received in revised form
1 May 2015
Accepted 2 May 2015

Keywords:
Early menopausal symptoms
Hop (*Humulus lupulus L.*)
Menopause
Randomized clinical trial

ABSTRACT

Objective: This study aimed to evaluate the efficacy of Hop on early menopausal symptoms and hot flashes.
Methods: In this randomized controlled trial, 120 women were randomly allocated into two groups, receiving the Hop or placebo tablets for 12 weeks. Early menopausal symptoms were assessed using Greene scale and hot flashes were recorded in a diary before, and 4, 8 and 12 weeks after intervention.
Results: The mean Greene score was significantly lower in the Hop group than the placebo group at the end of weeks 4 (adjusted difference: -10.0, 95% confidence interval: -11.1–-8.9), 8 (−18.6, -20.1–-17.1) and 12 (−23.4, -25.1–-21.6). The number of hot flashes was significantly lower in the Hop group than the control group during the weeks 4 (−8.4, -9.8–-7.1), 8 (−17.1, -14.9–-19.3) and 12 (−23.8, -21.1–-26.4).
Conclusions: Hop effectively reduced the early menopausal symptoms.
Clinical trial registration: This study was approved (code 91209) by the Ethic Committee of Tabriz university of Medical Sciences and registered at the Iranian registry of clinical trials, with IRCT 2013010110324N7 on April 2013.

1. Background

Menopause refers to permanent cessation of menstruation that occurs averagely at age 51; this period is characterized by amenorrhea [1]. The most common and specific symptom of menopause is hot flashes. The symptoms occur periodically as flushing, sudden sweating and chills, palpitation, anxiety, feeling pressure in head and chest, feeling flushed and intense heat, nausea, choking, and failure to focus [2]; these can disturb social activities, leisure, sleep, mood, focus, communication, sexual activity, and quality of life [3].

According to a large cross-sectional study in America, 57% of postmenopausal women and 49% of women in the premenopausal period showed significant symptoms of hot flashes [4]. In a study in Iran, 80% of women experienced moderate to severe and 10% mild flushing [5]. Hot flashes occur in approximately 75% of women during perimenopause and in most women last for 1–2 years after menopause, however it can continue up to 10 years or more [6].

The average life expectancy of women in Iran is estimated as 74.6 years [7] and according to the World Health Organization-2011, life expectancy of women at birth in 46 countries is more than 80 years [8], therefore, by increasing life expectancy, probably more women will encounter with menopausal complications such as increased blood cholesterol, cardiovascular diseases, osteoporosis, bone fractures, and even Alzheimer [9]. Therefore, study and treatment of menopausal problems has gained more importance.

Hormone therapy is a method of relieving early symptoms of menopause, but it may be associated with side effects and risks such as stroke, thromboembolic events, breast cancer, and vascular diseases, thus hormone-taking women need to be followed continuously [10]. According to a very large study performed for 5.6 years in 40 centers in the United States and comprised more than 27 thousand 50–79 years old postmenopausal women, combined hormone therapy is not recommended to treat symptoms of menopause [11]. Therefore, the use of alternative and complementary therapies is somewhat expanded [12]. Among alternative

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http://dx.doi.org/10.1016/j.ctcp.2015.05.001
1744-3881/

and hormonal treatments, herbal medicine including phytoestrogens (estrogen-like compounds) has gained a special place in treatment of menopausal symptoms [2]. According to a research carried out in Iran, only 9% of menopausal women used hormone therapy [13].

Phytoestrogens with three main categories of flavonoid, coumestan, and lignan are herbal compounds with estrogenic activity. Their chemical structure consists of two phenolphthaleins which can bind to estrogen receptor [14]. Phytoestrogens reduce the risk of cardiovascular diseases, breast and endometrial cancer, and osteoporosis, relief menopausal symptoms, especially hot flashes, and improve memory performance and sleep patterns. Low incidence of cardiovascular diseases in part of Asian population who consume phytoestrogens-containing diet demonstrates their protective effects [2,15].

Hop is a plant that contains phytoestrogens including prenylnaringenin as the most powerful phytoestrogen known to date [16]. Hop is 8 times stronger than other herbal estrogens. These phytoestrogens can bind to both estrogen receptors in the body and exert anticancer and antioxidant activities [17]. Hop is a dioecious, perennial, herbaceous climbing plant in the Cannabaceae family with thick fleshy roots, underground stems, and opposite, serrated leaves consisting of 3–5 unequal lobes. Its organs are covered with coarse fibers (containing lupulin) and it contains linalool, tannin, and resin [3,18]. When taken orally, the herb has hormonal activity [19].

The impact of hop on symptoms of menopause has been studied in a placebo-controlled double-blind study in Belgium (2006) which reported its effect on reducing vasomotor and other menopausal symptoms after 6 and 12 weeks. However, the drug was prescribed in this study as 100 μg extract in capsule. It was also stated that no specific dosage is identified currently to reduce symptoms and further research seems necessary in this regard [20]. Thus, we decided to investigate the impact of hop on early symptoms of menopause (primary outcomes) and hot flashes number (secondary outcome).

2. Methods

2.1. Study design and participants

This study was a double-blind controlled randomized clinical trial. It was performed in 2013 in health centers of Tabriz-Iran, on 40–60 years postmenopausal women (minimum 12 months and maximum 5 years after the last menstrual bleeding) and premenopausal women (with less than 12 periods during the last 12 months) who complained of hot flashes and had Greene scale scores of 15 and 42.

Exclusion criteria were illiteracy and inability to answer questions, not having cell phone for follow-up, consumption of sulfonamides, methotrexate, triamterene, sulfasalazine, estrogen, phenytoin, anxiolytics, anti-depressants, daily medicines and multivitamin, hormone therapy, use of OCP during the last 3 months, complementary alternative herbs to relieve vasomotor symptoms during the last month, hormone therapy contraindications including suspected or diagnosed breast or endometrial cancer, abnormal and undiagnosed genital tract bleeding, thromboembolic active disorders, liver or gallbladder active disease, lactose intolerance, and use of anti-thyroid drugs and other traditional medicines such as flushing-causing drugs (such as breast cancer medicines such as Letrozole, Raloxifene, Amlodipine, Bethanecol, Desmopressin and Calcitonin).

According to the study of Yasui et al. [21], and considering $m_1 = 18.3$ (mean of total score of menopause early symptoms before intervention), $m_2 = 15.5$ (assuming a 15% reduction in total score of menopause early symptoms), and $SD_1 = SD_2 = 4.9$, the sample size was calculated as 54 people for each group and considering the possibility of 10% loss, 60 subjects were estimated finally for each group.

2.2. Data collection tools

Data collection tools included a demographic questionnaire, the Greene Scale, and the recording checklist of hot flashes number.

The Greene Scale was devised by Professor Greene in Scotland and its reliability and validity has been proved [22]. The scale independently measures menopause-related mental, physical, and vasomotor symptoms. It includes 21 questions related to symptoms of menopause and each symptom is scored by the answerer as follows; no symptom as zero, little symptom as 1, moderate symptom as 2, and severe symptom as 3. Items 1–11 include psychiatric symptoms and are divided into two parts of anxiety (items 1–6) and depression (items 7–11), items 12-18 measure menopause physical symptoms, items 19 and 20 measure vasomotor symptoms, and item 21 measures sexual dysfunction [23,24].

2.3. Sampling

For sampling, at first 20, out of 90, health centers and bases were selected in Tabriz city-Iran with the highest number of patients, however, it was tried to select centers with different socio-cultural conditions. Then all premenopausal women were selected through their file (women up to menopausal age have a record in health centers and bases) and postmenopausal women were presented to the researcher by health liaisons; the researcher called and invited these subjects if they were qualified. In addition, health care employees were asked to inform the researcher in case of refers of eligible women. At the first visit, a written informed consent was obtained from participants after explaining the objectives and methodology of the study. The pretest questionnaires (demographic questionnaire and the Greene Scale) were completed by the participants; they were enrolled in the study if the score of the Greene Scale was more than 15 and less than 42.

2.4. Intervention

The participants were divided into two groups of intervention and control through randomized blocking with block sizes of four and six and allocation ratio of 1:1. To conceal the allocation of drug and placebo, they were put in closed opaque envelopes which were numbered serially. Each participant received three small envelopes each containing a month's supply of medication; these small envelopes were put in large opaque pockets numbered consecutively. Blocking and preparation of the pockets were performed by a person uninvolved in sampling and data analysis.

Each hop tablet is about 650 mg that contains 500 mg of Hop plant (the powdered flowering part of the plant, corymb), in which, it's contains 100 μg of the active ingredient. The main ingredient of the tablet is powdered hop plant's corymb that contains phytoestrogen. Hop tablets (powdered inflorescence of Hop, 5% gelatin solution, and avicel) and placebo (powdered lactose, 5% gelatin solution, and avicel) were similar in terms of shape, size, color, and odor. In order to achieve these similarities, red and blue permitted food additives were used, which led to consistent flavor and aroma.

Thus the data collectors, the participants, and the data analyzers were unaware of the type of intervention and the allocation of the individuals in the groups.

All participants in the intervention group received a Hop tablet daily for 90 days. Prior to intervention, a small pocket containing Hop or placebo and the checklist of hot flashes number during the